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A comparison of gold vs silver electrode contacts for high-resolution gastric electrical mapping using flexible printed circuit board arrays

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Abstract

Stomach contractions are initiated and coordinated by electrical events termed slow waves, and slow wave abnormalities contribute to gastric motility disorders. Recently, flexible printed circuit board (PCB) multi-electrode arrays were introduced, facilitating high-resolution mapping of slow wave activity in humans. However PCBs with gold-contacts have shown a moderately inferior signal quality to previous custom-built silver-wire platforms, potentially limiting analyses. This study determined if using silver instead of gold contacts improved flexible PCB performance. In a salt-bath test, modestly higher stimulus amplitudes were recorded from silver PCBs (mean 312 s.d. 89 μ V) than gold (mean 281 s.d. 85 μ V) ($p < 0.001$); however the signal to noise ratio (SNR) was similar ($p = 0.26$). In eight in-vivo experimental studies, involving gastric serosal recordings from five pigs, no silver vs gold differences were found in terms of slow wave amplitudes (mean 677 vs 682 μ V; $p = 0.91$), SNR (mean 8.8 vs 8.8 dB; $p = 0.94$) or baseline drift (NMRS; mean 12.0 vs 12.1; $p = 0.97$). Under the prescribed conditions, flexible PCBs with silver or gold contacts provide comparable results in-vivo, and contact material difference does not explain the performance difference between current-generation slow wave mapping platforms. Alternative explanations for this difference and the implications for electrode design are discussed.

Keywords

slow waves; multi-electrode; isochronal mapping; activation mapping

1. Introduction

Stomach contractions are initiated and coordinated by an underlying electrical activity, termed slow waves, which are generated and propagated by the interstitial cells of Cajal (ICCs) (Farrugia, 2008). In the human stomach, slow waves originate from a pacemaker site near the greater curvature of the gastric corpus, and propagate distally at a frequency of around three cycles per minute (cpm) (Hinder et al, 1977, O'Grady *et al.*, 2010a). Abnormalities of ICCs and slow waves are widely thought to contribute to gastric motility

disorders, such as gastroparesis, a condition involving unpleasant symptoms such as nausea, vomiting and abdominal bloating (Farrugia, 2008),(Ordog, 2008).

The recognition that ICC loss is associated with gastric motility disorders has renewed clinical interest in evaluating slow wave activity in affected patients and animal models. An important technical advance toward this aim has been the advent of high-resolution (HR) gastrointestinal (GI) electrical mapping. This strategy involves the placement of spatially-dense arrays of many electrodes (typically >100) over the electrically-active GI tissue and simultaneously recording from all sites (Lammers *et al.*, 1993). Graphical 'activation maps' are generated from these recordings, to accurately represent the spatiotemporal patterns of GI electrical propagation (Lammers *et al.*, 2009, Du *et al.*, 2009). While HR mapping has been used for many years in cardiology (Shenasa *et al.*, 2009), it has only recently started to make an impact in GI research, with several recent studies applying it to reveal important new insights into normal and abnormal slow wave behaviors (Lammers *et al.*, 2009), (Lammers *et al.*, 2008),(Egbuji *et al.*, 2010).

A novel electrode array was recently developed and validated for GI HR mapping based on flexible printed circuit board (PCB) electrode technology (Du *et al.*, 2009). The advantages of this type of array are that it can be rapidly constructed, readily sterilized, and the arrays can be mass produced with high-fidelity and low cost. The arrays are now being effectively applied in animal studies (O'Grady *et al.*, 2010b, Egbuji *et al.*, 2010), and they have recently also enabled the first HR description of human gastric slow wave activity (O'Grady *et al.*, 2010a).

However, a significant issue with the flexible PCB electrodes is that they achieve a modestly inferior signal quality compared to that of the alternative custom-built (shielded resin-embedded silver-wire) arrays that have been used in several previous animal studies by Lammers *et al* (2008, 2009, Du *et al.*, 2009). While the signal quality achieved by the flexible PCBs has been generally acceptable for most applications to date, it is an important detail because it can lead to uncertainties when analyzing regions of relatively low amplitude activity (e.g., from human corpus), particularly when background noise is relatively high. In addition, the accuracy of automated slow wave marking systems may be reduced when applied to recordings from PCBs, compared to recordings from the custom built arrays (Erickson *et al.*, 2010).

One possible explanation for the difference in recording quality between the flexible PCB arrays and the custom-built (shielded resin-embedded) arrays is that the flexible PCBs used to date have had gold electrode contacts, whereas the custom-built arrays have been fabricated using silver wires. Gold was chosen in the original flexible PCB design because it is the standard industrial contact material, whereas silver is less commonly used, and because silver potentially suffers from oxidation problems, whereas gold is inert. In general, silver is also less biocompatible than gold (Robinson *et al.* 1961). However, silver does have well-known advantages over gold as a bioelectrode material for signal transduction, notably: a more ideal electrode potential, a low level of intrinsic noise, a small value of charge transfer resistance (relatively non-polarizable) and a small interface impedance (McAdams *et al.* 2006, Malkin *et al.* 2002, Lapatki *et al.* 2004).

This study aimed to determine whether the flexible PCB arrays could be enhanced by using silver instead of gold as the contact material for slow wave mapping. Importantly, this study will therefore also define whether baseline data recorded using gold-contact flexible PCBs (e.g., Egbuji *et al.*, 2010, O'Grady *et al.*, 2010a) can be compared directly to any future data that may be acquired using silver-contact flexible PCBs, or whether a calibration factor would be necessary.

2. Methods

2.1 Electrode Design and Preparation

Three flexible PCB electrode designs were used in this study: two designs with gold contacts and one with silver contacts (Figure 1). Other than the electrode contacts, all designs were made from the same materials: copper channels in a polyimide ribbon base, and gold socket-connectors at the plug ends that were manually soldered to a standard 68 straight-pin SCSI (Small Computer System Interface) plug (Du *et al.*, 2009). The same solder material (60/40 SnPb) was used for all PCBs. Each flexible PCB array had 32 electrodes per recording head.

The recording array of the first gold-electrode design was identical to that used in several experimental studies to date, having an inter-electrode distance of 7.6 mm in a 4×8 configuration (O'Grady *et al.* 2010, Egbuji *et al.* 2010) (Figure 1A). The second gold-electrode design was identical to the silver-electrode design, having an inter-electrode distance of 4 mm, set in a 16×2 array (Figure 1B,C). The contact electrode size for all three designs was 0.3 mm, hence all of the gold recordings can be considered equivalent and no distinction is made in the analyses.

It is the practice in some institutions to 'chloride' pure silver electrodes prior to use, such as by soaking them in a solution such as bleach prior to rinsing and use, in order to improve the stability of electrical recordings (McAdams *et al.* 2006). Because it is intended that the methods of this study should inform human work, toxic substances such as bleach were not employed for any of these experiments. Chloriding can also be achieved by soaking the electrodes in an NaCl solution. For human operative applications, however, the sterilized flexible PCBs are unpackaged and arranged at the time of the incision, and are typically used immediately after laparotomy, meaning there is limited time available for NaCl soaking (O'Grady *et al.*, 2010a). Saline soaking was therefore also not performed in this study. A thin film of NaCl rich tissue fluid naturally covers the GI tract serosa, which is critical to achieving quality recordings, and gauze heavily soaked in warmed 0.9% NaCl solution was packed over the flexible PCBs to prevent drying. A 3-5 minute settling period in this context was then allowed before recordings were taken.

2.2 Salt-Bath Study Methods

A salt-bath study was performed first to compare the signal qualities of the gold and silver electrodes in a free solution. A 256 electrode patch was formed by alternating four silver and four flexible PCB arrays in a column (Figure 2A), and the patch was immersed in a sodium-chloride bath (0.9% solution). Electrical current was delivered via two stainless steel clips that sat directly opposite the middle of the PCB patch (~equidistant from silver and gold

patches), attached to a DS8000 stimulator (World Precision Instruments, Sarasota, FL): pulse width 1s, pulse amplitude 10 mA, period 5 s; square pulses. A 5 minute stabilization period was allowed, followed by 5 minutes of recordings.

2.3 In-Vivo Experimental Methods

A total of eight in-vivo comparison studies were undertaken in five weaner pigs. Ethical approval was granted by The University of Auckland Animal Ethics Committee, and these animals were subsequently reused in other work. The anesthetic and surgical methods were identical to those used in our other recent porcine studies (Egbuji *et al*, 2010, O'Grady *et al*, 2010b).

The recordings with the gold and silver PCB electrodes were taken simultaneously, and always from the anterior corpus and distal fundus. A recent study has shown no significant differences in slow wave properties (velocities, amplitudes and wave morphologies) between these two adjacent gastric regions in the pig (Egbuji *et al*, 2010), hence all electrodes were sitting on comparable tissue. Consecutive gold and silver arrays were arranged as per Figs. 2A,B, and these were held in position using warmed saline-soaked gauze. A settling period of 2-5 minutes was allowed, followed by recordings of 5-10 minutes duration.

2.4 Signal Acquisition and Analysis

Unipolar recordings were acquired from the PCBs via the ActiveTwo System (Biosemi, Amsterdam, The Netherlands), which was modified for passive recordings, at a recording frequency of 512 Hz. The common-mode sense (reference) electrode (CMS) was placed on the lower abdomen, and the right-leg drive electrode (DRL) was placed on the hind leg; slow wave recordings are referenced to the potential of the CMS electrode. The CMS and DRL were connected to standard 3M Ag/AgCl Red Dot cutaneous monitoring electrodes (3M, St Paul, MN). Each PCB was connected to the ActiveTwo via a 1.5 m 68-way ribbon cable, which was in turn fiber-optically connected to a notebook computer. The acquisition software was written in Labview 8.2 (National Instruments, Austin, TX).

All signal analysis was performed in Matlab v.2006b (The Mathworks, Natick, MA). Recordings were down-sampled to 30 Hz, and pre-processed by applying a Savitzky-Golay smoothing filter (polynomial order = 9; window size 6.6 s), to remove high-frequency noise (Savitsky *et al*, 1964). Three measures were used to quantify and compare the quality of recordings between the gold and silver electrodes: (i) slow wave amplitude; (ii) signal content; and (iii) baseline wander. The first step was to estimate the baseline wander of the raw recorded signal, using a 5 second moving average window. The baseline wander was quantified using the normalized root mean square error (NRMS; dimensionless) (Equation 1), and it was then removed from the raw signal.

$$NRMS = \frac{\sqrt{\frac{\sum_{i=1}^{n_b} b_i^2}{n_b}}}{b_{max} - b_{min}} \quad \text{Equation 1}$$

where b_i is the estimated baseline signal at time-step i and n_b is the length of the estimated baseline signal b , while b_{max} and b_{min} are the maximum and minimum values of the estimated baseline signal.

Individual slow wave events within the signal were then detected using the falling edge variable threshold (FEVT) algorithm, which was recently developed and validated for this purpose (Erickson *et al* 2010). Next, the signal content was defined by comparing the signal within a 3 s window at the FEVT-detected events with the remainder of the signal, which was regarded as the noise, as per a logarithmic scale of signal to noise ratio (SNR) (Equation 2). The slow wave amplitudes were defined by the difference in the peak and trough located 1.5 s either side of the FEVT-detected events.

$$SNR (dB) = 20 \log_{10} \left(\frac{\sqrt{\frac{\sum_{i=1}^{n_S} S_i^2}{n_S}}}{\sqrt{\frac{\sum_{i=1}^{n_N} N_i^2}{n_N}}} \right) \quad \text{Equation 2}$$

where S_i is the signal of interest at time-step i (i.e., slow wave events as detected by FEVT) and n_S is the length of the digitized signal of interest S , while N_i is the noise contained in the signal at time-step i (i.e., segments without FEVT-detected events) and n_N is the digitized length of N .

Statistical comparisons of gold vs silver outcomes were performed using the paired Students' t-test (significance threshold $p < 0.05$) and 95% confidence intervals of the significant outcomes are reported where appropriate.

Activation maps were also generated from the FEVT-marked activation times, as previously described (Du *et al*, 2009), and these were reviewed to ensure that the events being analysed were physiologically consistent with normal slow wave activity.

3. Results

Recordings from the silver and gold electrodes appeared qualitatively similar when used in both the salt bath and on the porcine gastric serosa. Isochronal activation maps of slow wave propagation were readily constructed (Fig 2C). Figure 2D shows representative slow wave recordings from silver and gold electrodes, prior to the subtraction of baseline drift.

In the salt bath study, configured as per Fig 2A, modestly higher stimulus amplitudes were recorded by the silver electrodes (mean 312 s.d. 89 μV) than the gold electrodes (mean 281 s.d. 85 μV) over >1500 events (mean difference 31 μV ; [CI: 25, 36]; $p < 0.0001$). However,

no overall difference was noted between the electrodes in terms of SNR (silver: mean 3.9 s.d. 0.4 dB vs gold: mean 3.9 s.d. 0.3 dB; $p=0.26$).

The results of the eight individual in-vivo experimental comparison studies (box-whisker plots) and the summary statistics (mean $\pm$ 95%CI) are presented in Figures 3-5. The in-vivo performance of the gold and silver contact PCB arrays was determined to be similar, with no differences found in terms of the slow wave amplitude, the signal content (SNR) or the baseline wander. The mean slow wave amplitudes were 677 [CI: 572, 782] μ V in the silver arrays and 683 [CI 556, 809] μ V in the gold arrays ($p=0.91$) (Figure 3). The SNR was 8.8 [CI: 6.7, 10.9] dB for the silver arrays vs 8.8 [CI: 7.0, 10.7] dB for the gold arrays ($p=0.94$) (Figure 4). The baseline drift (NMRS; dimensionless) was calculated at 12.0 [CI: 6.2, 17.7] for the silver arrays vs 12.1 [CI: 6.0, 18.2] for the gold arrays ($p=0.97$) (Figure 5).

4. Discussion

This study has compared silver and gold electrode contacts for flexible PCB electrodes used in the HR mapping of GI slow wave activity. A salt bath study was first conducted, followed by eight in-vivo experimental studies in five porcine subjects. While a minor performance difference in favor of the silver contacts could be determined in the salt bath, no practical difference in recording quality was found in-vivo in terms of the slow wave amplitudes, signal content (SNR) or the baseline wander in the recorded data.

These results are valuable because they will guide the design of future GI HR mapping electrodes. Under these specific test conditions (tailored to safe practicable human use), comparable slow wave recordings can be expected using flexible PCBs with either silver or gold contacts. Importantly, any future data acquired using silver-contact PCBs can therefore be fairly compared with the recently-established baseline data provided using gold-contact PCBs (Egbuji *et al.* 2010, O'Grady *et al.* 2010a), if the recording systems and methods are otherwise similar. These results may also be informative to cardiac researchers employing flexible PCB electrodes for cardiac mapping, however the generally higher signal amplitudes encountered in that field means that gold electrodes have been found to be highly satisfactory (e.g., Zhou *et al.* 2002).

Silver outperformed gold in the salt-bath study. This was expected, because as stated in the introduction, silver has several advantages for bioelectrode applications over gold, particularly when used as silver-silver chloride electrodes (McAdams *et al.* 2006, Lapatki *et al.* 2004). It was therefore somewhat surprising that we could not demonstrate a performance advantage for silver contacts over gold for in-vivo slow wave recordings. It is apparent that the minor advantages of silver electrodes do not significantly matter when evaluated in the context of all of the other biological and technical factors that influenced in-vivo slow wave signal acquisition in this study.

The previous comparison between gold-contact PCBs and custom-built (resin-embedded) silver-wire arrays was made from simultaneous recordings in experimental animals, using the same ActiveTwo System and setup described here, and electrodes of the same contact area (Du *et al.* 2009). If the contact metal type is not accountable for the improved signal quality of the custom built arrays, then what factors are responsible? One important factor

may have been the limited scope for chloriding the silver PCBs in this study, due to the constraints imposed by their major intended application in the human intra-operative setting. Superior cable construction is another potential explanation, for two reasons. Firstly, the custom-built array cables previously used for HR slow wave mapping have comprehensive shielding (e.g., Lammers *et al.* 2009, O'Grady *et al.* 2009), whereas the PCB cabling was not shielded (Du *et al.*, 2009). Secondly, the custom-built array cables have fewer contact junctions between the recording surface and the acquisition box than the PCB setup; signal quality may be degraded across these junctions. These problems are not straightforward to address, because in practice several key advantages of the flexible PCB electrodes (rapid and low-cost mass production, ease of safe sterilization, potential disposability) are likely to be diminished if more complex cabling is introduced. However, cabling improvements may nevertheless be required in future studies when a higher signal quality is demanded by the physiological purpose. Slight gains in signal quality are also theoretically possible from using a more highly conductive solder (e.g., the 96S composition) (Henkel Technologies 2007).

The choice of the most appropriate metal for any particular bioelectrode application depends on several important technical and practical factors other than signal quality (McAdams *et al.* 2006, Malkin *et al.* 2002). It is widely recognised that gold, silver and platinum are among the most ideal contact metals for recording bio-electrical events. Steel is less ideal, but has been used for almost a century to record GI slow waves, since Alvarez first used folded piano wires to record slow waves in the early 20th century (Berkson *et al.*, 1932). Stainless steel wires offer excellent material properties compared to silver and gold, which are soft metals. Ag-AgCl is the most ideal contact material for bioelectric signal transduction, and in future, customized flexible PCB electrode platforms with sintered Ag-AgCl contacts could be developed and trialed, like those described for body surface electromyography by Lapatki *et al.* (2004).

Given the equivalent results in this study, we will prefer the use of gold electrode contacts to silver in our experimental context. The primary reason is that gold is relatively inert, whereas silver suffers oxidation problems, which we have observed to limit the lifespan of the silver-contact PCBs. This is especially pertinent in human use, because low-temperature sterilisation methods rely on oxidizing agents such as ozone and hydrogen peroxide. In addition, we have also observed more ready depletion of the silver contact surface during gastric stimulation and pacing trials. Silver is also less biocompatible than gold, potentially causing a more pronounced host response, although this is more relevant to implant devices (McAdams *et al.* 2006, Robinson *et al.* 1961).

Although the modestly lower recording quality of the flexible PCBs has not been a substantial problem to date in experimental studies, it has recently become a more significant issue with the presentation of an accurate automated method for detecting slow wave activation times (Erickson *et al.*, 2010). This method (FEVT) achieves a highly satisfactory sensitivity (~94%) and positive predictive value (~93%) when detecting slow waves in data recorded with the custom-built silver-wire arrays, but a somewhat reduced sensitivity (~90%) and positive predictive value (~89%) when detecting slow waves in data recorded from the PCB arrays (Erickson *et al.*, 2010). These results were achieved after

individualized algorithm parameter tuning for both platforms (Erickson *et al.*, 2010). Therefore, investigators using the PCB arrays will have relatively more false positive and relatively fewer true positive slow wave activation times as a result, necessitating more time spent in manually correcting these outcomes. This issue may not be such a problem where signal quality is relatively high (e.g., in human antrum), but where amplitudes are low (e.g., in the human corpus), it will be more significant.

In summary, comparable results are found from using silver contacts instead of gold contacts for flexible PCB electrodes used in in-vivo GI HR slow wave mapping. Future results obtained using either contact metal in flexible PCB electrodes will be comparable, provided the recording and analysis systems are otherwise similar. Investigators must consider a balance of several factors when deciding which GI HR mapping setup to use for their particular need, including: cost, ease of use, method of application, need for sterilization, expected amplitude of the events in the target tissue, biocompatibility, and desired performance from automated analysis systems.

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Figure 1.

Three flexible PCB electrode designs were used in this study. Two had gold contacts (A,B), while one had silver contacts (C). The two gold contact flexible PCBs differed only in the electrode spacing and configuration as shown; in all cases the contact electrode size was 0.3 mm and results from the two gold electrodes are therefore equivocal.

Figure 2.

A) A typical configuration of flexible PCB arrays employed in this study; arrays of 32 silver and gold electrodes were staggered vertically (256 electrodes total; area $\sim 36 \text{ cm}^2$). **B)** In-vivo recordings were taken from the anterior porcine gastric corpus in the position shown. **C)** Activation map showing the slow wave propagation pattern across this gastric region. The colored (isochronal) bands represent the area of slow wave propagation per 1 s of time. The waves propagated distally and the lesser curvature half of the array is over quiescent tissue (Egbuji et al, 2010). **D)** Sample electrograms showing slow waves recorded from the silver and gold-contact flexible PCBs prior to removal of baseline drift.

Figure 3. Box-whisker plots for slow wave amplitude are shown for the eight in-vivo porcine studies, and summary statistics are given on the right. No difference was demonstrated.

Figure 4. Box-whisker plots for SNR are shown for the eight in-vivo porcine studies, and summary statistics given on the right. No difference was demonstrated.

Figure 5. Box-whisker plots for baseline drift (NRMS; dimensionless) are shown for the eight in-vivo porcine studies, with summary statistics given on the right. No difference was demonstrated.